

value is determined using parallel turbidity determinations. Essentially, the Thompson references teaches that a MIC can be determined by measuring turbidity and fluorescence simultaneously on parallel samples. Specifically, the Examiner refers to the following passage beginning at column 12, line 2 through column 12 line 17:

“Parallel control panels with the same antibiotics and organism, but no SR101 or resazurin were also set up. The dye containing panels were followed via fluorescence (FIG. 11). The other panel was read using visible turbidity at 18 hours as a measurement of growth. The penicillin Minimal Inhibitory Concentration, or MIC, was found to be 2 ug/ml for both the dye pair and turbidometric systems. The MIC is the lowest antibiotic concentration that inhibits macroscopic growth of the test organism, and is a measure of the sensitivity of the strain to the particular antibiotic. In the fluorometric determination (FIG. 10), the fluorescence in wells that grow parallel that of the no penicillin positive control, while inhibited wells show no significant fluorescence increase over the test period. The penicillin MIC for this organism could be determined as early as three hours using the dye pair technique. “ (Emphasis added)

Thus, what Thompson teaches at the cited passage is a *comparison* between two methods of determining a MIC value run in parallel, one turbimetric, and one fluorescent. NOT, as in the case of the present invention, a test system where one method is used to determine an organism's identity (a fluorescent method) performed in parallel with a separate method used to determine a MIC value (a turbimetric process). Thompson also teaches a fluorescent method for determining a microorganism's identity using a fluorescent technique, specifically, at column 12, lines 25-50. Moreover, the as the Examiner correctly points out, Thompson teaches (actually speculates) that either the ID or the MIC system could be automated.

However, unlike the present invention Thompson does NOT teach a combination system using a first technique for determining a microorganism's ID and a second technique for establishing an antimicrobial MIC for the same organism wherein the MIC method is turbimetric AND under the direction of an algorithm as presently claimed.

The algorithm of the present invention provides the automated assay system a method for assuring that the MIC is only read and reported at the appropriate time to

avoid reporting false antimicrobial sensitivity to the clinician. Furthermore, the present invention, unlike the Thompson disclosure, is designed to perform numerous MIC assays on multiple drugs simultaneously reporting each out only if the parameters of the algorithm have been met for each individual antimicrobial tested. There is nothing in the Thompson reference that would suggest such a sophisticated system having the capacity to read, score, store, re-incubate if necessary and ultimately determine accurately, for multiple antimicrobials, the correct MIC value while also being capable of determining the microorganism's identity (ID) in parallel using a separate assay methodology.

The Examiner has cited the Fischer Biotechnology Catalogue as evidence of the fact that a modified plastic microtiter plate was in existence at the time the present application was filed. The Applicant respectfully acknowledges this fact. However, merely disclosing a plastic microtiter plate does nothing to cure the deficiencies delineated above in Thompson relative to the claims as submitted in this Preliminary Amendment.

The Examiner has also cited Clark et al. (WO 98/53301) and states that Clark teaches an apparatus and method for determining a microorganism's identity simultaneously with an antimicrobial MIC in parallel, on the same plate using a range of methodologies including absorption, turbidity and fluorescent techniques. However, Clark does not teach the use of the algorithm disclosed and claimed in the present invention. Moreover, the Clark reference does not suggest the need for such an algorithm to assure accurate MIC values.

The clinical utility of prior automated ID/MIC systems has been limited by the need for continuous human intervention, or relying on protracted incubation times prior to reading MIC results. The present invention eliminates this need by providing a combination ID/MIC automated system termed the "Walkaway®" in recognition of this feature. Briefly, after the combination ID/MIC plates are inoculated they are placed in an incubation chamber where they are maintained at a predetermined temperature. At preprogrammed intervals readings are taken of the individual wells using fluorescent techniques for ID and turbidity measurements for the MIC. The system has been standardized such that the IDs are read at a set time and the information stored in a

database. The MIC plates are read continuously and the growth in drug containing wells is constantly compared with control wells pursuant to the algorithm of Figure 1. The present invention allows each MIC well to be read individually and the data collated with control wells. As each MIC value becomes reliable, it is stored along with the ID and reported simultaneously with the ID after all MIC values are ready, or individually as needed in emergency situations. By continuously monitoring the plates, accurate MIC values and organism IDs become available in the shortest period of time with minimal human intervention.

Thompson teaches a manual method and suggests that it may be automated. It does not teach an automated system using the algorithm of the present invention. The Fisher Biotechnology Catalogue merely teaches a plastic plate suitable for use in turbidimetric and/or fluorescent assays. Cooke teaches an automated microbial ID/MIC system but does not disclose an algorithm-based system of the present invention. One of the fundamental requirements of any prima facie 35 U.S.C. §103(a) rejection is that the combination of references, taken as a whole, suggest the modification to the person of ordinary skill in the art. *In re Napier*, 34 USPQ2d 1782 (Fed. Cir. 1995). In the present case, nothing suggests the need for an algorithm to assure accuracy in automated MIC determining systems.

Moreover, the prior art references, specifically Thompson and Cooke teach "rapid" methods but do not stress the need for accuracy or suggest how MIC accuracy is controlled, as is in the case of the present invention which relies on the algorithm of claim 43. Furthermore, the CAFC has held that all claim limitations must be considered especially when that element is missing from the prior art. In *In re Fine* 5 USPQ 2d 1596 (Fed. Cir. 1988) the court held that a reference, or combination of references, do not render the claimed combination prima facie obvious when a material claim limitation is absent. In the present case, the algorithm, used in combination with the device and methods of the present invention, is material and is not disclosed in any of the prior art references. Therefore, the Applicants respectfully assert that based on the arguments above and new claims 43-51, the cited references, Thompson, Fisher and Cooke do not meet the standard for rendering the claims as submitted for consideration obvious.

Additionally, there is no suggestion in the cited prior art that an algorithm as presently claimed would even be necessary in order to arrive at accurate, clinically relevant MIC values. Consequently, the absence of any suggestion of an algorithm in the references, taken individually or in their totality, means that a person of ordinary skill in the art would have to divine the present algorithm (and the need for one) from the body of analogous prior art and/or their own personal knowledge. The Examiner has not provided any reference or affidavit that would support an assertion that there would have been a reasonable expectation that an ordinarily skilled artisan would have successfully invented the algorithm-based ID/MIC system of the present invention based on the state of the prior art at the time the present invention was conceived. Therefore, the Applicant respectfully asserts that absent a showing that persons of ordinary skill in the art recognized a need for controlling automated ID/MIC devices using an algorithm and that combining such algorithms with automated ID/MIC devices was suggested in the art, a prima facie case of obviousness as it relates to the present claims cannot be made.

Finally, the Applicants note that the Examiner has correctly cited MPEP 2144.04.III, August 2001 that the mere automation of a manual activity for the same result is not sufficient to distinguish over the prior art. However, in the present case the Applicant has not merely automated a manual process. The present inventor has invented a method for providing highly precise MIC values for microorganisms in parallel with determining the microorganisms' identification. This has been made possible, in part, through the combined application of the novel algorithm of the present invention and surprising discovery that the turbidity measurements made using the present invention achieved a previously unrecognized level of precision and sensitivity thus allowing for rapid, accurate MIC values that are predictive of in vivo clinical outcomes.

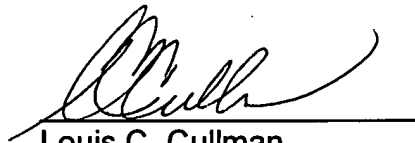
In conclusion, the Applicants respectfully assert that regardless of how the cited references are combined, taken as a whole they fail to teach or suggest the present invention such that a person having ordinary skill in the art would have had a reasonable expectation of achieving what the present inventors have now claimed. Moreover, knowledge generally available to those having ordinary skill in the art of

antimicrobial testing in combination with the cited references (collectively the "the prior art") would have merely suggested to an ordinarily skilled investigator a route of virtually endless experimentation and random trial and error investigations before discovering the algorithm claimed and used it in present microorganism ID/MIC system. In essence, only by using the present invention disclosure as a road map for his hindsight could one having ordinary skill in the art have found the novel solution to the problem of performing rapid and accurate microorganism IDs and MICs in a single automated "walkaway" system as provided by the present invention. Therefore, the Applicant respectfully asserts that the invention as presently claimed, taken in its totality, is not prima facie obvious and therefore asks that the Examiner to allow these claims and permit this application to issue.

If for any reason direct communication with Applicants' attorney would serve to advance prosecution of this case to finality, the Examiner is invited to call the undersigned attorney at the below listed telephone number.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 16-2230.

Respectfully submitted,



Louis C. Cullman
Registration No. 39, 645

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OPPENHEIMER WOLFF & DONNELLY LLP
840 Newport Center Drive, Suite 700
Newport Beach, CA 92660
Telephone: 949.823.6000
Facsimile: 949.823.6100